REMARKS

The present invention relates to methods for treating a subject in need of increased natriuretic peptide function. The methods comprise administering one or more inhibitors of prolyl-specific DPP to the subject in an amount sufficient to inhibit degradation of the natriuretic peptide.

Claims 29-33 and 43-46 are pending in the application. Applicant respectfully requests reconsideration of the claimed invention in view of the following remarks.

1. Rejection of claims 29, 32, and 43 under 35 U.S.C. § 102

Applicant respectfully traverses the rejection of claims 29, 32 and 43 under 35 U.S.C. § 102(e) as being anticipated by Haffner *et al.*, US2004/0167341.

Applicant submits herewith a declaration under 37 C.F.R. §1.132 of Ian Reilly, M.D., to address certain aspects of Haffner *et al.*, referred to in the following remarks as "the Reilly declaration."

A. *Haffner et al. does not disclose the step of selecting a subject to receive one or more inhibitors of prolyl-specific dipeptidyl peptidase based a diagnosis of congestive heart failure, as recited by the present claims*

The Haffner *et al.* patent application is cited for allegedly "teach[ing] a method for treating congestive heart failure by administering to a patient a compound that inhibits a dipeptidyl peptidase, including DPP-IV. See page 3, sections 0027-0028." Office Action, page 3. Applicants respectfully submit that the Haffner *et al.* patent application, when properly considered together with the knowledge of one skilled in the art, does not disclose the step of selecting a subject to receive one or more inhibitors of prolyl-specific dipeptidyl peptidase ("DPP") based upon a diagnosis of congestive heart failure, as recited in the present claims.

As discussed in the Reilly declaration, ¶ 5, the Haffner *et al.* patent application is directed to "novel compounds... for inhibiting serine proteases... such as dipeptidyl peptidase IV." The section of Haffner *et al.* referred to by the Examiner in the rejection states the following (emphasis added):

> The present invention also includes a method of inhibiting a post proline/analine cleaving protease comprising administering a compound of the present invention as herein described. Preferably, the post proline/analine cleaving protease is a serine protease. Preferably, the serine protease is a dipeptidyl peptidase. In one aspect preferably the dipeptidyl peptidase is DPP-II. In another aspect preferably the dipeptidyl peptidase is DPP-IV.
>
> The present invention also includes a method for the treatment or prophylaxis of metabolic disorders, gastrointestinal disorders, viral disorders, inflammatory disorders, diabetes, obesity, hyperlipidemia, dermatological or mucous membrane disorders, psoriasis, intestinal distress, constipation, autoimmune disorders, encephalomyelitis, complement mediated disorders, glomerulonepritis, lipodystrophy, tissue damage, psychosomatic, depressive, and neuropsychiatric disorders, HIV infection, allergies, inflammation, arthritis, transplant rejection, high blood pressure, congestive heart failure, tumors, and stress-induced abortions comprising administering a compound of the present invention as herein described. Preferably, the compound of the present invention as herein described is administered for the treatment or prophylaxis of diabetes, more preferably Type II diabetes.

It is important to note that this section of Haffner *et al.*, in addition to being nothing more than a long "wish list" encompassing literally hundreds of conditions, does not inform the skilled artisan whether a particular cited condition is treatable directly, prophylactically, or potentially by both approaches by administering a DPP inhibitor. Instead, this section refers to treatment or prophylaxis in the alternative for the specified conditions as a group, leaving unclear whether any individual condition may be treated directly, indirectly by prophylaxis or may be addressed using both approaches. Reilly declaration, ¶ 6.

Thus, one cannot properly conclude from the passage relied on by the Examiner in Haffner *et al.* that this reference describes administration of a DPP inhibitor for the treatment of an existing condition of Haffner *et al.* As such, Haffner *et al.* explicitly disclose the step of selecting a subject based upon a diagnosis of congestive heart failure. Reilly declaration, ¶ 6.

Furthermore, there is other evidence in Haffner *et al.* and elsewhere that runs counter to the Examiner's assertion that this reference describes the use DPP inhibitors to treat an existing case of congestive heart failure. In paragraph [0002] of the Background of the Invention section, Haffner *et al.* indicates that "[a]s examples of the therapeutic value of DPP-IV, DPP-IV is believed to be involved in a variety of metabolic, gastrointestinal, viral, and inflammatory

diseases." The term "involved in" is a broad term that presumably includes conditions where DPP-IV is directly implicated in the disease (and hence is suitable for "treatment"), as well as those conditions where DPP-IV is involved because it is implicated in a precursor to the disease (and hence is suitable for "prophylaxis"). As indicated in the Reilly declaration, ¶ 7, while Haffner *et al.* indicates that DPP-IV is believed to be "involved in" congestive heart failure, the question unanswered by Haffner *et al.* is "how."

When viewed in this light, it is apparent that the Examiner's belief that Haffner *et al.* teaches a method for treating congestive heart failure by administering a dipeptidyl peptidase inhibitor is unfounded. Moreover, Haffner *et al.* does not teach the step of selecting a subject based a diagnosis of congestive heart failure. Accordingly, the anticipation rejection should be withdrawn.

B. *Haffner et al. does not provide an enabling disclosure with regard to selecting a subject to receive one or more inhibitors of prolyl-specific dipeptidyl peptidase based a diagnosis of congestive heart failure, as recited by the present claims*

As discussed in *Impax Laboratories, Inc. v. Aventis Pharmaceuticals Inc.*, 468 F.3d 1366, 1381-82 (Fed. Cir. 2006), in order to be anticipating, a prior art reference must be enabling so that the claimed subject matter may be made or used by one skilled in the art. Prior art is not enabling so as to be anticipating if it does not enable a person of ordinary skill in the art to carry out the invention. And enablement is effected only if one of ordinary skill in the art could have combined the publication's description of the invention with his own knowledge to make the claimed invention.

As in any enablement analysis, the factors addressed in addressed in *In re Wands*, 858 F.2d 731 (Fed.Cir.1988) are applied to the allegedly anticipatory reference to determine whether any experimentation required is undue. *See, Elan Pharmaceuticals, Inc. v. Mayo Foundation for Medical Educ. and Research*, 346 F.3d 1051, 1054-55 (Fed. Cir. 2003). When Haffner *et al.* is properly considered in view of the various *Wands* factors, it is apparent that Haffner *et al.* does not enable a person of ordinary skill in the art to carry out the invention as presently claimed. Accordingly, Haffner *et al.* is not properly citable as prior art to the present claims.

(i) The quantity of experimentation necessary

As discussed above, paragraph [0028] of Haffner *et al.* refers to "a method for the treatment or prophylaxis of metabolic disorders, gastrointestinal disorders, viral disorders, inflammatory disorders, diabetes, obesity, hyperlipidemia, dermatological or mucous membrane disorders, psoriasis, intestinal distress, constipation, autoimmune disorders, encephalomyelitis, complement mediated disorders, glomerulonepritis, lipodystrophy, tissue damage, psychosomatic, depressive, and neuropsychiatric disorders, HIV infection, allergies, inflammation, arthritis, transplant rejection, high blood pressure, congestive heart failure, tumors, and stress-induced abortions" (emphasis added). This section refers to treatment or prophylaxis in the alternative, without informing the skilled artisan of which conditions may be treated directly, and which may be addressed indirectly by prophylaxis. Reilly declaration, ¶ 6.

Haffner *et al.* presents an enormous list of diseases, the vast majority of which have no known direct relationship to DPP or to DPP inhibitors. In his declaration, Dr. Reilly refers by way of example to the categories underlined in the preceding paragraph: viral disorders, tissue damage, psychosomatic disorders, congestive heart failure, and tumors, and notes that Haffner *et al.* provides no description of any common pathophysiological basis offered by which the skilled artisan could reasonably believe DPP inhibitors would be of either a therapeutic or prophylactic benefit. Reilly declaration, ¶¶ 7 and 8. Indeed, a list of human viral disorders compiled by the American Society for Microbiology (a copy of which is provided in an appendix of this submission) continues for some 20 pages of text; and a list of human cancers (and so only a subset of the list of human tumors) compiled by the National Cancer Institute (a copy of which is provided in an appendix of this submission) includes 210 entries, albeit including some duplications.

For this reason, Dr. Reilly concludes that the skilled artisan would not consider it credible that DPP inhibitors may be used in treatment or prophylaxis of this vast array of diseases. Reilly declaration, ¶ 9. For the skilled artisan to determine which, if any, of the myriad conditions presented in Haffner *et al.* could potentially be used to select subjects for treatment, Dr. Reilly also concludes that the skilled artisan must embark on a research program in which each possible disease is considered in turn, with the mere hope of being successful. Reilly declaration, ¶ 10.

One would not simply focus on congestive heart failure in this regard, and there is no basis provided in Haffner *et al.* for selecting a subject on the basis of a diagnosis of congestive heart failure. The quantity of experimentation would be considered to be both large and unguided. Reilly declaration, ¶ 10.

(ii) the amount of direction or guidance presented

As noted above, for the vast majority of diseases listed in Haffner *et al.*, including congestive heart failure, there is no description of any common pathophysiological basis offered by which the skilled artisan could reasonably believe DPP inhibitors would be of either a therapeutic or prophylactic benefit. There is no guidance provided in Haffner *et al.* for selecting subjects on the basis of a diagnosis of congestive heart failure.

(iii) the presence or absence of working examples

Haffner *et al.* provides no examples in which congestive heart failure is addressed, either therapeutically or prophylactically.

(iv) the nature of the invention

The nature of the claimed invention is the delivery of therapeutic preparations, specifically DPP inhibitors, to subjects based on a particular disease diagnosis, specifically congestive heart failure.

(v) the state of the prior art

For the vast majority of conditions recited in Haffner *et al.*, including congestive heart failure, there was no known direct relationship of prolyl-specific DPP, or the use of prolyl-specific DPP inhibitors as therapy in subjects in the prior art. Reilly declaration, ¶ 7.

As Applicant discussed in a previous office action response, increasing natriuretic peptide levels had been found to provide therapeutic benefit to heart failure patients. NATRECOR® (human recombinant BNP) was approved by the U.S. FDA in 2001 for the intravenous treatment of patients with acutely decompensated congestive heart failure.

Neutral endopeptidase ("NEP") had been considered to be a key degradation mediator of BNP, and inhibitors of NEP enzymatic activity have also found use in treating patients with heart

failure. Moreover, a combination treatment with both BNP and NEP inhibitors has been reported to produce a synergistic effect on cardiac output, reduced vascular resistance, and unloading of the heart.

Human BNP, however, had been reported to be unusually resistant to NEP degradation. *See, e.g.*, Smith *et al.*, "Delayed metabolism of human brain natriuretic peptide reflects resistance to neutral endopeptidase," *J. Endocrinol.* 167:239-46 (2000). This resistance led those in the art to question the role of neutral endopeptidase inhibition (*e.g.*, Smith *et al.*, page 245, last sentence) in the treatment of heart failure. However, even after the filing date of the present invention, the identity of an alternative degradative pathway for BNP, while actively sought within the art, remained unknown. And certainly, there was no suggestion in the prior art that prolyl-specific DPP was involved in this metabolism. *See, e.g.*, Walther *et al.*, "Biochemical analysis of neutral endopeptidase activity reveals independent catabolism of atrial and brain natriuretic peptide," *Biol. Chem.* 385: 179-184 (2004):

> [O]ur data clearly indicate one or more other ANP- and BNP-degrading peptidases different from NEP at least in the heart, lungs, and kidneys. The nature of these peptidases is unknown until now, but they should not belong to the aminopeptidases and not be ACE, because bestatin and lisinopril did not influence NP [natriuretic peptide] degradation.

(vi) the relative skill of those in the art

The general level of skill in the art with regard to the use of DPP inhibitors in the treatment of metabolic diseases (diabetes) is high. As indicated by Applicant previously, a large number of such molecules are in clinical trials, with one (Januvia) approved by the U.S. FDA for glycemic control in type 2 diabetes.

(vii) the predictability or unpredictability of the art

Haffner *et al.* presents an enormous list of diseases, the vast majority of which had no known direct relationship to DPP or to DPP inhibitors. Reilly declaration, ¶¶ 7 and 8. The use of prolyl-specific DPP inhibitors as therapy in subjects diagnosed as having such diseases, including congestive heart failure, was unpredictable prior to Applicant's invention, as no reasoned scientific basis for such uses could be gleaned from the art. For the skilled artisan to determine

which, if any, of the myriad conditions recited in Haffner *et al.* could potentially be used as a basis to select subjects for treatment, the skilled artisan must embark on a research program in which each possible disease is considered in turn with no scientific basis on which to predict success. Reilly declaration, ¶ 10.

(viii) the breadth of the claims

The breadth of conditions recited in Haffner *et al.* can best be described as covering the substantial entirety of human medical conditions. Reilly declaration, ¶ 9. In stark contrast, the present claims are directed to the delivery of DPP inhibitors to subjects based on a particular diagnosis, specifically congestive heart failure.

(ix) conclusion

The present claims include a step of selecting a subject for treatment based upon a specific diagnosis; that is, congestive heart failure. Haffner *et al.* presents a large "wish list" of conditions, stating that these conditions might be suitable for treatment or prophylaxis. The skilled artisan considering conditions that might serve as a basis for selecting a patient for treatment with a DPP inhibitor is faced with Haffner *et al.*'s list that can best be described as covering the substantial entirety of human medical conditions. In the absence of any working examples or reasoned scientific basis for considering DPP inhibitors to be directly useful in such conditions, the skilled artisan must address each and every condition hoping to identify those that could be directly treated with DPP inhibitors. Rather than an enabling disclosure, Haffner *et al.* would represent nothing more than an invitation to experiment. Determining which, if any, of these conditions could be used in order to select subjects for delivery of DPP inhibitors would require undue experimentation in the form of a *de novo* clinical research program.

As such, it cannot reasonably be stated that this reference is enabled with regard to the present claims that require selection of subjects on the basis of a diagnosis of congestive heart failure. Accordingly, the anticipation rejection should be withdrawn because Haffner *et al.* is not properly citable as prior art to the present claims.

C. *The present invention is novel and distinct from the methods disclosed in Haffner et al.*

As Applicant discussed in a previous office action response, the present invention lies in Applicant's identification of a new use of prolyl-specific DPP inhibitors. Specifically, because natriuretic peptides such as B-type natriuretic peptide ("BNP") are substrates for hydrolysis by prolyl-specific DPPs, DPP inhibitors may be used as a direct treatment of ongoing congestive heart failure.

The present invention solves, at least in part, the search for alternative degradative pathways for natriuretic peptides in humans. As described in paragraph [0046], natriuretic peptides, and BNP specifically, represent suitable substrates for prolyl-specific DPPs. Pharmaceutically acceptable amounts of the various prolyl-specific DPP inhibitors known in the art, including those described in paragraphs [0126] and [0127] of the specification, may be used to inhibit this previously unknown degradative pathway for natriuretic peptides. And because of the relationship of natriuretic peptides, and BNP specifically, to heart failure, subjects may be selected for administration of prolyl-specific DPP inhibitors based on a diagnosis of congestive heart failure.

In view of the foregoing, Applicant respectfully submits that no *prima facie* case of anticipation has been established, and urges the Examiner to withdraw the anticipation rejection of claims 29, 32, and 43.

2. Rejection of claims 30 and 44 under 35 U.S.C. § 103

Applicant respectfully traverses the rejection of claims 30 and 44 under 35 U.S.C. § 103(a) as being obvious in view of Haffner *et al.* in view of De Meester *et al., Biochem. Pharmacol.* 54: 173-79, 1997.

The deficiencies in the Haffner *et al.* publication are described in detail above, and are not repeated here. De Meester *et al.* is cited solely for the disclosure of a DPP inhibitor comprising a phophonate moiety. As such, De Meester *et al.* does not cure the deficiencies in the primary Haffner *et al.* publication. Haffner *et al.* and De Meester *et al.*, whether considered alone or in combination, fail to teach or suggest the step of selecting subjects for administration of prolyl-specific DPP inhibitors based on a diagnosis of congestive heart failure.

Applicant respectfully submits that no *prima facie* case of obviousness has been established, and urges the Examiner to withdraw the anticipation rejection of claims 30 and 44.

3. Rejection of claims 31 and 45 under 35 U.S.C. § 103

Applicant respectfully traverses the rejection of claims 30 and 44 under 35 U.S.C. § 103(a) as being obvious in view of Haffner *et al.* in view of Bergmann *et al.*, U.S. Patent 6,756,483.

The deficiencies in the Haffner *et al.* publication are described in detail above, and are not repeated here. Bergmann *et al.* is cited solely for the disclosure of a DPP inhibitor comprising an antibody or antibody fragment. As such, Bergmann *et al.* does not cure the deficiencies in the primary Haffner *et al.* publication. Haffner *et al.* and Bergmann *et al.*, whether considered alone or in combination, fail to teach or suggest the step of selecting subjects for administration of prolyl-specific DPP inhibitors based on a diagnosis of congestive heart failure.

Applicant respectfully submits that no *prima facie* case of obviousness has been established, and urge the Examiner to withdraw the anticipation rejection of claims 31 and 45.

4. Rejection of claims 33 and 46 under 35 U.S.C. § 103

Applicant respectfully traverses the rejection of claims 30 and 44 under 35 U.S.C. § 103(a) as being obvious in view of Haffner *et al.* in view of Mills *et al.*, J. Am. Coll. Cardiol. 34: 155-62, 1999.

The deficiencies in the Haffner *et al.* publication are described in detail above, and are not repeated here. Mills *et al.* is cited solely for the disclosure that human recombinant B-type natriuretic peptide is used therapeutically in congestive heart failure. As such, Mills *et al.* does not cure the deficiencies in the primary Haffner *et al.* publication. Haffner *et al.* and Mills *et al.*, whether considered alone or in combination, fail to teach or suggest the step of selecting subjects for administration of prolyl-specific DPP inhibitors based on a diagnosis of congestive heart failure.

Applicant respectfully submits that no *prima facie* case of obviousness has been established, and urge the Examiner to withdraw the anticipation rejection of claims 33 and 46.

CONCLUSION

Applicant respectfully submits that the pending claims are in condition for allowance. An early notice to that effect is earnestly solicited. Should any matters remain outstanding, the Examiner is encouraged to contact the undersigned at the address and telephone number listed below so that they may be resolved without the need for additional action and response thereto.

Respectfully submitted,

Date 10/26/2007

By _____

FOLEY & LARDNER, LLP
P.O. Box 80278
San Diego, CA 92138-0278
Telephone: (858) 847-6721
Facsimile: (858) 792-6773

Richard J. Warburg, Registration No. 32,327
Attorney for Applicant
By Barry S. Wilson, Registration No. 39,431